13. Support for Claim 58 can be found on page 4, lines 1-3 and page 9, lines 29-30 while support for Claim 59 can be found on page 4, line 4. As the amendments to the claims are fully supported by the specification as originally filed and add no new matter, entry is in order.

The Examiner has alleged the Declaration is defective as the filing date of the provisional application to which the present application claims priority is incorrect. A new Declaration has been prepared and is submitted herewith.

The Examiner has alleged Applicants have not complied with one or more conditions for receiving benefit of an earlier filing date under 35 U.S.C. §119(a)-(e) as the application contains no reference to the provisional application. The specification, as amended, contains a reference to provisional application Serial No. 06/062,994, filed October 23, 1997. Thus, Applicants have complied with the conditions of receiving benefit of the earlier filing date of October 23, 1997, and the Applicants respectfully request that the Examiner acknowledge this compliance.

According to Claim 27 the invention is directed to a method for mediating intramolecular recombination in eukaryotic cells, comprising the step of providing eukaryotic cells with prokaryotic beta recombinase and its specific target sequences. The prokaryotic beta recombinase is capable of using factors provided by the eukaryotic cells in order to exhibit recombinase activity.

According to Claim 28 the invention is directed to a method for mediating intramolecular recombination in chromatin structures of eukaryotic cells, comprising the step of providing eukaryotic cells with prokaryotic beta recombinase and its specific target sequences. The prokaryotic beta recombinase is capable of using factors provided by the eukaryotic cells in order to exhibit recombinase activity.

According to Claim 43 the invention is directed to a method for catalysing site-specific resolution of DNA sequences in an extrachromosomal target introduced into an eukaryotic cell, comprising the step of catalysing the site-specific resolution with beta recombinase. The eukaryotic cell provides factors which beta recombinase is capable of using in order to exhibit recombinase activity.

According to Claim 58 the invention is directed to a method of promoting beta recombinase activity comprising the step of providing beta recombinase with eukaryotic cells factors which the beta recombinase is capable of using in order to exhibit recombinase activity.

Claim 28 has been objected to due to informalities. The Examiner alleges "eukaryotes" is misspelled. Claim 28 has been amended, whereby the objection has been overcome.

Claims 27 and 31-50 have been rejected under 35 U.S.C. §112, first paragraph, as not being supported by an enabling specification. The Examiner alleges the specification, while being enabling for a method of using beta recombinase in mammalian cells containing HMG1 protein, does not reasonably provide enablement for all eukaryotic cells. The Examiner alleges there is a strict requirement for E. coli HU and/or mammalian HMG1 proteins for the site-specific recombination catalyzed by beta recombinase. The Examiner further alleges that the Applicants do not demonstrate that the beta recombinase is capable of mediating site-specific combination in the absence of one of these proteins.

As will be set forth in detail below, Applicants submit that Claims 27, 31-33 and 35-50 are supported by an enabling specification. Accordingly, the rejection is traversed and reconsideration is respectfully requested.

Claims 27 and Claims 31-33 and 35-42 dependent directly on indirectly thereon, and Claim 43, and Claims 44-50 dependent directly on indirectly thereon, recite methods wherein the prokaryotic beta recombinase is capable of using factors provided by the eukaryotic cells in order to exhibit recombinase activity. Attention is directed to page 9, lines 3-30 of the specification, which discusses results indicating beta recombinase is active in a eukaryotic environment using the machinery/factors provided by a host cell. Additionally, Claim 53 recites a method according to Claim 27, wherein the factors provided by the eukaryotic cells comprise HMG1 chromatin-associated protein.

Thus, Claims 27, 31-33 and 35-50 are enabled by the specification, whereby the rejection has been overcome.

Claim 28 has been rejected under 35 U.S.C. §112 as not being supported by an enabling specification. The Examiner alleges Claim 28 is drawn to method for controlling gene expression, and that the breadth of the claim is broad, encompassing the up and/or down regulation of a gene permanently and/or transiently. The Examiner further alleges the specification teaches a method by which using beta recombinase to generate a recombination event one could alter the expression of a gene by deletion, however, the specification is silent with respect to the specific sequence to be deleted and the consequential effect on the gene expression.

As will be set forth in detail below, Applicants submit that Claim 28 is supported by an enabling specification. Accordingly, the rejection is traversed and reconsideration is respectfully requested.

Claim 28 has been amended to recite a method for mediating intramolecular recombination in chromatin structures of eukaryotic cells. The method comprises the step of providing eukaryotic cells with prokaryotic beta recombinase and its specific target sequences, wherein the prokaryotic beta recombinase is capable of using factors provided by the eukaryotic cells. Attention is directed to page 9, lines 3-30 of the specification, which discusses results indicating beta recombinase is active in a eukaryotic environment using the machinery/factors provided by a host cell, and to page 10 lines 2-30, which discloses that beta recombinase promotes recombination in chromatin structures.

Therefore, Claim 28 is supported by an enabling description, whereby the rejection has been overcome.

Claim 52 has been rejected under 35 U.S.C. §112, first paragraph, as not being supported by an enabling specification. The Examiner alleges the breadth of the claim encompasses a method of producing transgenic animals with any and all animals from the animal kingdom, including mammals, reptiles, amphibians, birds, insects and other invertebrates. The Examiner further alleges the specification does not teach production of any transgenic animals, and there is no description or working examples of the use of embryonic stem cells known in the art to be capable of giving rise to whole animals. The Examiner additionally alleges that the Applicants admit that a transgenic mouse model is under development, indicating the method to develop transgenic animals is not enabled.

As will be set forth in detail below, Applicants submit that Claim 52 is supported by an enabling specification. Accordingly, the rejection is traversed and reconsideration is respectfully requested.

Claim 52 recites a method according to Claim 27 for development of transgenic mammal cells, further comprising the step of selecting the eukaryotic cells from the group consisting of mammalian cells. As indicated by the specification on page 1, lines 21-22, techniques for development of transgenic mouse strains and gene targeting technologies are known. Further,

the specification sets forth methods of preparing transgenic simian cells based on COS-1 cell line (page 5, lines 11-20), and teaches that beta recombinase can accurately and efficiently catalyse site-specific recombination in mammalian genomes (page 10, lines 25-29).

Therefore, Claim 52 is supported by an enabling description, whereby the rejection has been overcome.

Claims 27, 28, 31, 33-42, 48, 50 and 52 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

As will be set forth below, Applicants submit that Claims 27-28, 31, 33, 35-42, 48, 50 and 52 are definite. Accordingly, the rejection has been traversed and reconsideration is respectfully requested.

The Examiner alleges Claim 27 is unclear in its recitation of "transgenic work" and is a method claim but contains no method steps. Claim 27 has been amended to delete the term "transgenic work". Present Claim 27 recites a method of mediating intramolecular recombination eukaryotic cells, comprising the step of providing eukaryotic cells with a prokaryotic beta recombinase in its specific sequence, wherein the prokaryotic beta recombinase is capable of using factors provided by the eukaryotic cells. Thus, Claim 27 recites a method step, whereby the claim is definite.

The Examiner has alleged Claim 28 is a method claim but contains no method steps. Claim 28, as amended, recites a method for mediating intramolecular combination in chromatin structures of eukaryotic cells, and recites the step of providing eukaryotic cells with prokaryotic beta recombinase and its specific target sequences wherein the prokaryotic beta recombinase is capable of using factors provided by the eukaryotic cells. Thus, Claim 28 recites a method step, whereby the claim is definite.

The Examiner has alleged Claim 33 is vague and unclear in its recitation of "two or more different specific recombination events at a time". The Examiner has alleged the specification is clear that the presence of beta recombinase results in a recombination event between two intramolecularly located *six* sites, and it is unclear how two or more different events could occur in this context.

Claim 33 has been amended to clarify a method wherein two or more recombination events involving different DNA sequences occur at the same time, wherein each DNA sequence is located between target sequences. Thus, Claim 33 is definite.

The Examiner has alleged Claim 34 is unclear in its recitation of "exclusively". The Examiner alleges the specification teaches that in the context given in Claim 32, only the intramolecular reaction will occur, and to include exclusively in the claim implies that others may occur. The Examiner further alleges that if this is not the case, then Claim 34 does not further limit Claim 32. Claim 34 has been canceled.

The Examiner has alleged Claims 35-39 are unclear in their recitation of "laying" and that this is additionally grammatically incorrect. Claims 35-39 have been amended to recite that the DNA fragment is located between *six* sites or target sequences, whereby the rejection has been overcome.

The Examiner alleges that Claims 39-40 are unclear in their recitation of "specific recognition sequences". Claims 39-40 have been amended to recite "target sequences". As set forth in the specification on page 3, lines 29-31, target sequences is meant to include *six* sites or DNA sequences containing natural *six* sites or modified versions which allow recombination activity. Thus, Claims 39-40 are definite.

The Examiner has alleged that Claim 48 is indefinite in its recitation of "allocated". Claim 48 has been amended to recite "located", whereby Claim 48 is definite.

The Examiner alleges that in Claim 50 there is no antecedent basis for "the *six* sites". Claim 50 has been amended to provide proper antecedent basis, whereby Claim 50 is definite.

The Examiner alleges Claim 52 is an intended use for transgenic animals which does not further limit Claim 27 as no additional step is recited. Claim 52, as amended, recites a method according to Claim 27 for development of transgenic mammalian cells, and recites the additional step of selecting eukaryotic cells from the group consisting of mammalian cells. Thus, Claim 52 recites an additional step, whereby the claim is definite.

Therefore, for the reasons set forth above, Applicants submit that Claims 27-28, 31, 33, 35-42, 48, 50 and 52 are definite, whereby the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

Applicants appreciate the Examiner's acknowledgment that all claims are free from art.

As set forth above, Applicants submit that Claims 27-33 and Claims 35-52, as well as Claims 53-60, are definite and supported by an enabling specification. Therefore, the Examiner is requested to withdraw the rejections of Claims 27-33 and 35-52 and to allow the application to pass to issue.

Respectfully submitted,

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